REMARKS

The Office Action lists claims 1 to 13 as pending. However, the pending claims are 1 to 18. Claims 14 to 18 are set forth on pages 3 and 4 of the AMENDMENT UNDER 37 CFR 1.111 dated November 21, 2002 (filed November 26, 2002).

The presently claimed invention concerns a therapeutic agent composition for a corneal epithelial disorder comprising a compound having an effect of activating Rho as an active ingredient and a pharmacological carrier.

The presently claimed invention is also directed to a method of treating a corneal epithelial disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound having an effect of activating Rho.

Claims 1 to 13 were rejected under 35 USC 112, first paragraph, for allegedly failing to comply with the written description requirement. The reasons for the 35 USC 112 rejection are set forth on page 2 of the Office Action.

The rejection concerns the terminology in the claims of "a compound having an effect of activating Rho."

It is admitted in the Office Action that the specification discloses examples of structures of some compounds within the scope of what is claimed.

Applicants respectfully rebut the 35 USC 112 rejection on the basis of the following disclosures set forth in the specification:

(1) Firstly, as disclosed on page 4, lines 4 to 10 of the specification, in order to study the participation of Rho in the migration mechanism of the corneal epithelium, the present inventors conducted a pharmacological test regarding the effects of Rho inhibitors on the corneal epithelium. As a result, the inventors discovered that the corneal epithelial migration is almost completely inhibited when Rho is inhibited. See Table 1 at the middle of page 10 of the specification, as reproduced hereinbelow:

Table 1

	Migration length (μ m)
Control	454
Exoenzyme C3 (2 μ g/ml)	186

(Each datum in the table is an average of six samples.)

Table 1 shows that when the corneal block is cultured in Exoenzyme C3 which is a Rho inhibitor, corneal migration is almost completely inhibited.

From the above-mentioned findings, it is revealed that Rho, which is the low-molecular weight GTP-binding protein, participates in the migration mechanism of the corneal epithelium.

(2) Next, on the basis of the results of their tests, the inventors envisaged that compounds having Rho-activating effects would achieve excellent effects of promoting the corneal epithelial migration. Then, the inventors conducted pharmacological tests using oleoyl lysophosphatidic acid ("oleoyl LPA"), which is one of the compounds having Rho-activating effects, to confirm that compounds having Rho-activating effects provide excellent results with respect to promoting the corneal epithelial migration. See Table 2 at the top of page 11 of the specification, as reproduced hereinbelow:

Table 2

	Migration length (μm)
Control	454
Oleoyl LPA (0.02 μM)	528
(0.2 μM)	658
(2 μM)	712

(Each datum in the table is an average of six samples.)

Further, the inventors confirmed that when compounds having Rho-activating effects and Rho inhibitors were used jointly, the corneal epithelial migration was almost completely inhibited as long as Rho was inhibited. See Table 3 at the bottom of page 11 of the specification, as reproduced hereinbelow:

Table 3

	Migration length (μm)
Control	454
Exoenzyme C3 (2 μg/ml) + Oleoyl LPA (0.02 μM)	185
+ Oleoyl LPA (0.2 μM)	182
+ Oleoyl LPA (2 μM)	198

(Each datum in the table is an average of six samples.)

These results confirm that the corneal epithelial migration-promoting effect is based on the Rho-activating effect (see page 12, lines 2-3 of the specification).

In view of the above, it is respectfully submitted that one of ordinary sill in the art would readily understand from the disclosure of the present specification that compounds having Rho-activating effects would exhibit the desired effects of the present invention. Therefore, it is respectfully submitted that one having ordinary skill in the art can easily carry out the

invention as disclosed in the present specification and as recited in the present claims and that the present specification and claims meet all the requirements as set forth in 35 U.S.C. 112.

In view of the above, withdrawal of the 35 USC 112, first paragraph rejection is respectfully requested.

Claims 1 to 7 were rejected under 35 USC 102 as being anticipated by Liliom et al., Am Phys. Soc., 274, C1065-C1074 (1998), as indicated at the top of page 2 of the October 8, 2003 Office Action.

It is noted that the Office Action did not include any prior art rejection of claims other than claims 1 to 7. Thus, there was no prior art rejection in the October 8, 2003 Office Action for claims 8 to 18.

In the entire record of this application, the only reason given for rejecting applicants' claims over Liliom et al. is set forth at the middle of page 2 of the August 27, 2002 Office Action as follows: "Liliom et al. teach the use of lysophosphatic acid such as oleoyl lysophatidic acid...for the treatment of corneal wounds."

Liliom et al. tested the effect of oleoyl lysophosphatidic acid ("LPA") for promoting proliferation for only corneal

keratocytes. The present claims, however, relate to a therapeutic agent composition for a corneal **epithelial** disorder and to a method for treating a corneal **epithelial** disease. The present invention does not relate to corneal disorders of keratocytes.

Thus all of the disorders recited in applicants' claims 4 to 7 of corneal ulcer, corneal erosion, keratitis and dry eye are symptoms caused by corneal **epithelial** defects.

Although Liliom et al. tested the effect of oleoyl lysophosphatidic acid ("LPA") for promoting proliferation for corneal keratocytes, Liliom et al. did not test for an effect of LPA on corneal **epithelial** cells (see columns 1 and 17 of Liliom et al.). The presently claimed invention is novel, since Liliom et al. do not teach or suggest an effect of LPA for (i) promoting proliferation for corneal **epithelial** cells and (ii) therapeutic effects on corneal **epithelial** disorders.

The cornea consists mainly of an epithelial layer, a stromal layer and an endothelial layer. The thickness of the epithelial layer is about one tenth as thick as that of the cornea, whereas the thickness of the stromal layer is about nine tenths as thick

as that of the cornea. The corneal epithelial layer protects the eyeball from external stimulation as a barrier to shut-off the corneal stromal layer from outside of the eyeball, whereas the corneal stromal layer participates in the maintenance of water in the cornea and greatly affects transparency of the cornea. The corneal epithelial layer has a five- to six-layer structure of corneal epithelial cells, and the cells are changed in a turnover of about one week. On the other hand, the corneal stromal layer has keratocytes, which are mesenchyme cells, scattered in the stromal layer consisting of an extracellular matrix, and it is said that a turnover of the keratocytes takes two to three years. Accordingly, corneal **epithelial** cells are substantially different from keratocytes in structure, function, etc.

Attached to applicants' AMENDMENT UNDER 37 CFR 1.111 dated November 21, 2002 was a copy of Steven E. Wilson et al., Investigative Ophthalmology & Visual Science, July 1993, Vol. 34, No. 8, 2544-2561, which describes on pages 2554 and 2555 that EGF (epidermal growth factor) has effects for promoting the proliferation for all of epithelial cells, keratocytes and endothelial cells of the cornea (see Figs. 8 and 9 of Wilson et al.). On the other hand, it is shown that HGF (hepatocyte growth factor) and KGF (keratocyte growth factor) promote the proliferation of epithelial cells and endothelial cells, but does not promote the proliferation of keratocytes.

Since epithelial cells, keratocytes and endothelial cells of the cornea differ in structure and role, it is respectfully submitted that prior to the present invention, one of ordinary skill in the art could not have predicted whether or not compounds having an effect of activating Rho of the present invention would have an effect for promoting the proliferation of the corneal **epithelial** cells, until pharmacological tests are carried out.

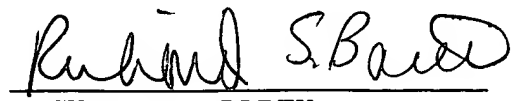
Withdrawal of the anticipation rejection in view of Liliom et al. is thus respectfully requested.

It is respectfully submitted that applicants' claimed invention is not anticipated and is not rendered obvious by the reference.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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